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CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1633	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	09/827,854	ZANNIS ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *83-101* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *83-101* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 10/03/07 was entered.

Amended claims 83-101 are pending in the present application, and they are examined on the merits herein **with SEQ ID NO: 15 (apoE3) and adenoviral vector as the previously elected species**. It is noted that SEQ ID NO: 2 is the mature apoE3 amino acid sequence, while SEQ ID NO: 15 is the apoE3 preproprotein containing its N-terminal signal peptide.

Response to Amendment

The rejection under 35 U.S.C. 112, first paragraph, for the lack of Written Description was withdrawn in light of Applicant's amendment.

The rejection under 35 U.S.C. 112, first paragraph, for enablement was partially withdrawn in light of Applicant's amendment.

Claim Objections

Amended claim 83 is objected to because of the phrase "**a secreted polypeptide consisting of** amino acid residues 1-185 of SEQ ID NO:2 or amino acid residues 1-185 of SEQ ID NO:2 and one or more amino acids 186-259 of SEQ ID NO:2". This is because a polypeptide consisting of the recited amino acids would not constitute a secreted polypeptide because it lacks a signal peptide. Appropriate correction is required.

Amended claims 96-97 and 101 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. This is because the polypeptide of claims 96-97 further includes a signal peptide, while the polypeptide in claim 83 from which both claims 96-97 are dependent upon consists only the recited amino acid residues of SEQ ID NO:2. The encoded polypeptide containing amino acids 1-277 of an apoE preprotein of any one of SEQ ID NOs. 14-19 (with SEQ ID NO. 15 is the elected species) is outside the amino acid range of the encoded polypeptide consisting of the recited amino acid residues of SEQ ID NO:2 in claim 83 from which claim 101 is dependent on.

New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Amended claims 83-97 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. ***This is a new ground of rejection necessitated by Applicant's amendment.***

Amended independent claim83 and its dependent claims recite the new limitation "**a secreted polypeptide consisting of amino acid residues 1-185 of SEQ ID NO:2 or amino acid residues 1-185 of SEQ ID NO:2 and one or more amino acids 186-259 of SEQ ID NO:2**". As written, the claims encompass the use of an encoded secreted polypeptide consisting of amino acid residues 1-185 of SEQ ID NO:2 and one or more amino acids 186-259 of SEQ ID NO:2 **in any combination as long as they are amino acids 186-259 of SEQ ID NO:2**, for example a secreted polypeptide consisting of amino acid residues 1-185 of SEQ ID NO:2 in contiguous with amino acids 186-200 of SEQ ID NO:2 or in contiguous with amino acids 186, 200 and 258 of SEQ ID NO:2, or in contiguous with amino acids 190, 195, 200, 210 and 233 of SEQ ID NO:2. The specification as originally filed does not provide any written support for a method of lowering cholesterol in a mammal in need thereof as now claimed. Applicants also failed to point out the specific page number and/or line number in the originally filed specification that provides written support for this new limitation in the Amendment filed on 10/3/07.

Therefore, given the lack of sufficient guidance provided by the originally filed specification, it would appear that Applicants did not contemplate or have possession of invention as now claimed at the time the application was filed.

Amended claim 101 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. ***This is a modified rejection necessitated by Applicant's amendment.***

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The specification teaches by exemplification showing the construction of recombinant adenoviruses expressing secreted apoE4 and various secreted truncated forms of apoE4 (e.g., apoE4-185, apoE4-202, apoE4-229, EpoE4-259). In an apoE-deficient mouse model, the recombinant adenoviruses were injected intravenously through the tail vein and the effects of full-length apoE4 and its various truncated forms on cholesterol and triglyceride homeostasis were evaluated. Applicants showed that an insignificant reduction of the mouse cholesterol level and a severely induced hypertriglyceridemia were observed in apoE-deficient mice treated with full-length apoE4-adenovirus, whereas reduced levels of cholesterol without the induction of hypertriglyceridemia were obtained in animals treated with recombinant adenoviruses expressing the aforementioned truncated forms of apoE4. Applicants further demonstrated that overexpression of either full-length apoE3 or apoE4 is sufficient to induce combined hyperlipedimia (high cholesterol and triglyceride levels) in normal

C57BL6 mice, whereas an overexpression of apoE4-202 has no detectable effect on triglyceride levels of the C57BL6 mice.

The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant broadly claimed invention for the following reasons.

(a) The breadth of the claim

The instant claim is directed to a method of lowering cholesterol in a mammal in need thereof without inducing hypertriglyceridemia, wherein said mammal expressing a functional low density lipoprotein (LDL) receptor, said method comprising intravascularly administering to said mammal a replication-defective adenoviral vector comprising a nucleic acid encoding amino acids 1-277 of an apoE preprotein of SEQ ID NO: 15 (the elected species containing SEQ ID NO:2).

(b) The state and the unpredictability of the art

The nature of the instant claims falls within the realm of gene therapy. At the effective filing date of the present application (4/6/2000), the state of the gene therapy art was and still remains unpredictable with respect to the attainment of desired therapeutic effects, for this instance lowering the total serum cholesterol level without inducing hypertriglyceridemia in a mammal expressing a functional LDL receptor, as evidenced by the reviews of Verma et al. (Nature 389:239-242, 1997; IDS), Dang et al. (Clin. Cancer Res. 5:471-474, 1999), Romano et al. (Stem Cells 18:19-39, 2000) and Kawashiri et al. (Curr. Control Trials Cardiovasc. Med. 1:120-127, 2000). Dang et al.

stated "Although significant progress has been achieved in our understanding of the limitations of gene therapy by suboptimal vectors, host immunological responses to the vectors, and the lack of long term stable expression, the major challenge that limits clinical translation remains in achieving efficient gene delivery to target tissues" (page 474, col. 2, last paragraph). Romano et al. stated "The potential therapeutic applications of gene transfer technology are enormous. However, the effectiveness of gene therapy programs is still questioned" (see abstract), and "Despite the latest progress reported in the area of vector design, research strategies still have to tackle critically important issues, such as further improvement of gene transfer technology, especially for *in vivo* gene delivery applications, regulation and control of the transgene expression post-cell transduction, and a variety of complex safety matters. These three main issues are to some extent intertwined and pose severe limitations on the applications of gene transfer technology in therapy" (page 21, col. 1, first paragraph). In October 2000, Kawashiri et al. still stated "Somatic gene therapy is a viable approach to the therapy of several lipid disorders for which therapies are currently inadequate" and "The next decade is therefore likely to witness several clinical trials of gene therapy for lipid disorders" (see Conclusion section, page 125). Kypreos et al. (FASEB J. 15:1598-1600, 2001) also stated "One major parameter in successful gene therapy approaches is **gene dosage** and **expression levels**....The inability of the truncated apoE forms that lack all or part of the carboxyl-terminal 260-299 region to induce hypertriglyceridemia, coupled with their intact ability to clear cholesterol, makes them attractive candidates in future gene therapy applications to correct remnant removal disorders" (page 1600, col.

2, last paragraph). Thus, it is clear that at the effective filing date of the present application gene therapy for the treatment of any lipid disorder was still immature and not routine.

Additionally, at the effective filing date of the present application (4/6/2000) although substantial evidence in the prior art as well as the findings of the present invention suggested or indicated that ApoE functioned **to decrease cholesterol while increasing triglyceride levels** (see references cited on page 6, lines 4-25 of the instant specification), the findings of Tsukamoto et al. (J. Clin. Invest. 100:107-114, 1997; Cited previously) and Kashyap et al. (J. Clin. Invest. 96:1612-1620, 1995) indicated that under their experimental conditions the infection of ApoE-deficient mice with a recombinant adenovirus capable of expressing a mature, full-length human ApoE (299 amino acid residues) resulted in **a reduction in the plasma total cholesterol level without an induction of hypertriglyceridemia**. Thus, at the effective filing date of the present application it was apparent that the biological activity of the ApoE proteins to maintain cholesterol and triglyceride homeostasis *in vivo*, at least in ApoE-deficient mice, was still unpredictable, let alone in any mammal expressing a functional LDL receptor.

The unpredictability of the biological activity of the ApoE proteins to maintain cholesterol and triglyceride homeostasis *in vivo* is further supported by the results of Yoshida et al. (Circulation 104:2820-2825, 2001) that showed that ApoE-deficient mice receiving apoE-/- bone marrow cells that express human apoE3 or apoE2 or apoEcys142 have cholesterol levels increasing with age and the cholesterol levels are not affected by apoE expression (see abstract). Interestingly, the lesion in male apoE3

mice was 40% smaller than that of control mice, while the lesion of apoE2 mice was similar to that of control mice and apoEcys142 mice showed an unexpected and significant increase in lesion size. It is further noted that ApoE2 differs from apoE3 by having a cysteine instead of an arginine at residue 158; and apoEcys142 contains 2 amino acid substitutions: an arginine substitution for cysteine at residue 142 and an arginine for cysteine substitution at residue 112.

(c) The amount of direction or guidance presented

Apart from the exemplification using an apoE-deficient mouse model with recombinant adenoviruses expressing secreted apoE4 or one of the secreted truncated apoE variants apoE4-185, apoE4-202, apoE4-229, EpoE4-259 (**all of these truncated apoE variants lack the carboxyl-terminal 260-299 region**), the instant specification fails to provide sufficient guidance for a skilled artisan on how to lower the total serum cholesterol level without inducing hypertriglyceridemia in a mammal using a replication-defective adenoviral vector encoding amino acids 1-277 of SEQ ID NO:15 as now claimed. The instant specification fails to provide sufficient guidance for a skilled artisan on which modification(s), for example deletion, insertion or substitution, in which combination(s), and at which amino acid residues in the carboxyl-terminal region of a mature, native, human apoE (amino acids 260-299) still possesses the desired property, for this instance lowering the total serum cholesterol level without inducing hypertriglyceridemia in a mammal expressing a functional LDL receptor. Additionally, at the effective filing date of the present application, there was no evidence of record in the present application or in the prior art indicating that an encoded apoE3-277 possesses

the ability to lower the total serum cholesterol level without inducing hypertriglyceridemia in a mammal expressing a functional LDL receptor. As is well recognized in the art, any modification (even a "conservative" substitution) to a critical structural region of a protein is likely to significantly alter its functional properties. Guo et al. (PNAS 101:9205-9210, 2004) estimated that only about a third of single amino acid changes would completely inactivate the average protein and increasing the number of substitutions additively increases the probability that the protein would be inactivated and that specific proteins may be more or less tolerant to changes (see the entire article). Moreover, even one year after the effective filing date of the present application, Applicants still state "**The identification of amino acid residues within the carboxyl terminal region of apoE, which mediate the hypertriglyceridemic effect of apoE, is the subject of ongoing research**" (Kypreos et al., J. Biol. Chem. 276:19778-19786, 2001; page 19785, col. 2, bottom of the first full paragraph). Furthermore, Yoshida et al. (Circulation 104:2820-2825, 2001) demonstrated that a single amino acid substitution between ApoE2 and ApoE3 proteins can have a significant effect in their biological acitivity *in vivo*, let alone for the breadth of the encoded secreted polypeptide to be utilized in the method as claimed.

As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most

chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues discussed above, the unpredictability of the gene therapy as well as the relevant art on the biological activity of apoE protein in lowering the total serum cholesterol level without inducing hypertriglyceridemia, and the breadth of the instant claims, it would have required undue experimentation for one skilled in the art to make and use the instant claimed invention.

The examiner notes that in the Amendment filed on 10/03/07 (pages 7-8), Applicants failed to address specifically the non-enablement issues direct specifically to the use of an encoded amino acids 1-277 of SEQ ID NO:15 for lowering cholesterol without inducing hypertriglyceridemia in a mammal expressing a functional low density lipopoprotein receptor in the Office Action mailed on 5/31/07 (pages 6-14).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Amended claims 83-86, 90-91 and 93-99 are rejected under 35 U.S.C. 102(b) as being anticipated by McClelland et al (WO 96/14837) as evidenced by Wetterau et al (J. Biol. Chem. 263:6240-6248, 1988) and Breslow et al (J. Biol. Chem. 257:14639-14641, 1982; Cited previously) for the same reasons already set forth in the Office Action mailed on 5/31/2007 (pages 16-18). ***The same rejection is restated below.***

McClelland et al discloses at least a gene therapy method for the treatment of hypercholesterolemia, said method comprises intravenous administering (e.g., portal vein injection or peripheral vein injection) a recombinant replication defective adenoviral vector containing a DNA sequence encoding a human apoliporotein E3 or **a fragment of human apoliporotein E3 that is truncated at the C-terminal** (page 4, line 5 continues to line 9 of page 6; page 9, third paragraph) in a mammalian host, including a human host (page 8, last paragraph). **The C-terminal of a human apolipoprotein E3 is made up of amino acid residues 225-299 as evidenced by the teachings of Wetterau et al** (see at least the abstract). Therefore, the encoded human apolipoprotein E3 fragment that is truncated at the C-terminal that is taught by McClelland et al is an encoded human apolipoprotein E3 fragment that lacks amino acid residues 225-299. Additionally, the DNA sequence encoding human apolipoprotein 3 or its fragment may further include a leader sequence or portion thereof, a secretory signal or portion thereof of the apolipoprotein E gene (page 5, first paragraph). McClelland et al teaches specifically that **a clone having a perfect match with the expected sequence encoding human apoliporotein E3 with the Genbank accession #K00396 was used** (page 11, last sentence of first paragraph). The sequence

encoding human apoliporotein E3 with the Genbank accession #K00396 is the same sequence reported by Breslow et al that has 100% sequence identity to SEQ ID NO:15 (SEQ ID NO:2 plus its signal sequence) of the present invention as evidenced by the teachings of Breslow et al. (see at least Fig. 3 and the attached sequence search). It is also noted that McClelland et al also teach the use of other human apoliporotein E isoforms or allelic variants (page 4, fourth and fifth paragraphs). McClelland et al further teaches that hypercholesterolemia is often associated with cardiovascular disease such as atherosclerosis (page 9, second paragraph), and that the method can be used to treat apolipoprotein-deficient animals, including apoE-deficient animals (page 9, last paragraph). McClelland et al also discloses that the reduction of plasma cholesterol concentrations and changes in the plasma lipoprotein distribution was presumably a result of the association of the human apoE protein with both apoB48- and apoB100-remnant lipoprotein particles, thereby increasing removal from the circulation (page 22, last sentence). Please noted that the DNA sequence encoding a fragment of human apolipoprotein E3 that is truncated at the C-terminal taught by McClelland et al also encodes amino acids 1-203 and/or 1-220 of SEQ ID NO:2.

Accordingly, the method taught by McClelland et al has the same method steps and the same starting materials as the instant broadly claimed methods. Therefore, the reference anticipates the instant claims.

Response to Amendment

Applicant's arguments related to the above rejections in the Amendment filed on 10/03/07 (pages 8-13) have been fully considered, but they are respectfully not found persuasive for the reasons discussed below.

Applicants argue basically that the McClelland et al reference fails to teach or suggest each and every limitation of the instant claims because it only describes generic apolipoprotein E fragments (i.e., those having unspecified deletions at the C-terminus and/or the N-terminus). Applicants highlighted the statement "Such fragments and derivatives of apolipoprotein E retain the same biological activity as unmodified apolipoprotein E" in a paragraph defining the term "fragment or derivative thereof" by McClelland et al. Applicants also argue that the Office improperly uses the Wetterau et al reference to expand the meaning of the term "fragments" as it is used by McClelland et al. to encompass apolipoprotein E fragments not even disclosed or conceived by McClelland et al. Applicants further argue that McClelland et al fails to teach or suggest even a single species within the broad genus of apolipoprotein E fragments, and thus the use of Wetterau et al reference is an improper use of a secondary reference in making a rejection under 35 USC 102. Moreover, the missing descriptive matter, for this instance apoE fragments lacking amino acids 225-299, is not necessarily present in the disclosure of McClelland et al because McClelland et al failed to describe the apoE fragment disclosed by Wetterau et al, while one of many possibilities, is not necessarily the one described by McClelland et al.

Firstly, the Office has not expanded the meaning of the term "fragments" as it is used by McClelland et al in any shape or form. McClelland et al disclosed clearly at least a gene therapy method for the treatment of hypercholesterolemia, said method comprises intravenous administering (e.g., portal vein injection or peripheral vein injection) a recombinant replication defective adenoviral vector containing a DNA sequence encoding a human apoliporotein E3 or **a fragment of human apoliporotein E3 that is truncated at the C-terminal** (page 4, line 5 continues to line 9 of page 6; page 9, third paragraph) in a mammalian host, including a human host (page 8, last paragraph). Please note that that the McClelland et al reference **does not teach** explicitly the use of a fragment of human apolipoprotein E3 that is truncated **at the C-terminus or C-terminal end** as argued by Applicants. Nor does the McClelland et al reference teach the use of **a fragment of human apolipoprotein E3 that is truncated within the C-terminal**. The examiner simply relied on the Wetterau et al. reference for what is known in the prior art for the term "the C-terminal of apolipoprotein E3". **"The C-terminal" of a human apolipoprotein E3 is made up of amino acid residues 225-299 as evidenced by the teachings of Wetterau et al** (see at least the abstract). **Therefore, the encoded human apolipoprotein E3 fragment that is truncated at the C-terminal taught by McClelland et al is an encoded human apolipoprotein E3 fragment that lacks amino acid residues 225-299**.

Secondly, such a fragment of human apolipoprotein E3 that is truncated at the C-terminal taught by McClelland et al **would retain the same biological activity as unmodified apolipoprotein E and consistent with the term "fragment or derivative**

thereof" defined by McClelland et al. Please note that Tsukamoto et al. (J. Clin. Invest. 100:107-114, 1997; Cited previously) and Kashyap et al. (J. Clin. Invest. 96:1612-1620, 1995) already showed that under their experimental conditions the infection of ApoE-deficient mice with a recombinant adenovirus capable of expressing a mature, full-length human ApoE (299 amino acid residues) resulted in **a reduction in the plasma total cholesterol level without an induction of hypertriglyceridemia**.

Accordingly, amended claims 83-86, 90-91 and 93-99 are still rejected under 35 U.S.C. 102(b) as being anticipated by McClelland et al as evidenced by Wetterau et al and Breslow et al for the reasons set forth above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended claims 83 and 91-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over McClelland et al (WO 96/14837) as evidenced by Wetterau et al (J. Biol. Chem. 263:6240-6248, 1988), Breslow et al (J. Biol. Chem. 257:14639-14641, 1982; Cited previously) and in view of French et al. (US 6,290,949) for the same reasons already set forth in the Office Action mailed on 5/31/2007 (pages 18-21). ***The same rejection is restated below.***

McClelland et al discloses at least a gene therapy method for the treatment of hypercholesterolemia, said method comprises intravenous administering (e.g., portal vein injection or peripheral vein injection) a recombinant replication defective adenoviral vector containing a DNA sequence encoding a human apoliporotein E3 or **a fragment of human apoliporotein E3 that is truncated at the C-terminal** (page 4, line 5 continues to line 9 of page 6; page 9, third paragraph) in a mammalian host, including a human host (page 8, last paragraph). **The C-terminal of a human apolipoprotein E3 is made up of amino acid residues 225-299 as evidenced by the teachings of Wetterau et al** (see at least the abstract). Therefore, the encoded human apolipoprotein E3 fragment that is truncated at the C-terminal that is taught by McClelland et al is an encoded human apolipoprotein E3 fragment that lacks amino acid residues 225-299. Additionally, the DNA sequence encoding human apolipoprotein 3 or its fragment may further include a leader sequence or portion thereof, a secretory signal or portion thereof of the apolipoprotein E gene (page 5, first paragraph). McClelland et

al teaches specifically that **a clone having a perfect match with the expected sequence encoding human apoliporotein E3 with the Genbank accession #K00396 was used** (page 11, last sentence of first paragraph). The sequence encoding human apoliporotein E3 with the Genbank accession #K00396 is the same sequence reported by Breslow et al that has 100% sequence identity to SEQ ID NO:15 (SEQ ID NO:2 plus its signal sequence) of the present invention as evidenced by the teachings of Breslow et al. (see at least Fig. 3 and the attached sequence search). It is also noted that McClelland et al also teach the use of other human apoliporotein E isoforms or allelic variants (page 4, fourth and fifth paragraphs). McClelland et al further teaches that hypercholesterolemia is often associated with cardiovascular disease such as atherosclerosis (page 9, second paragraph), and that the method can be used to treat apolipoprotein-deficient animals, including apoE-deficient animals (page 9, last paragraph). McClelland et al also discloses that the reduction of plasma cholesterol concentrations and changes in the plasma lipoprotein distribution was presumably a result of the association of the human apoE protein with both apoB48- and apoB100-remnant lipoprotein particles, thereby increasing removal from the circulation (page 22, last sentence).

McClelland et al does not teach specifically to administer the vector to an artery at the site of a lesion.

However, at the effective filing date of the present application, French et al already taught at least of direct intra-arterial injection or infusion of a recombinant replication defective adenoviral vector carrying gene sequences that are capable of

ameliorating symptoms of cardiovascular diseases such as atherosclerosis or dyslipidemia or restenosis in a mammal (see at least Summary of the Invention, particularly col. 5; and examples 6-7).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method of McClelland et al by also delivering the replication-defective adenoviral vector to an artery at the site of a lesion in a mammal suffering a cardiovascular disease such as atherosclerosis in light of the teachings of French et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because the specific localized gene delivery for ameliorating symptoms of cardiovascular diseases such as atherosclerosis or dyslipidemia or restenosis in a mammal using a recombinant replication defective adenoviral vector has been taught and successfully demonstrated by French et al.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of McClelland et al as evidenced by Wetterau et al, Breslow et al and in view of French et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Amendment

Applicant's arguments related to the above rejections in the Amendment filed on 10/03/07 (pages 13-21) have been fully considered, but they are respectfully not found persuasive for the reasons discussed below.

1. Applicants argue that McClelland et al reference is completely silent on the structure and sequence of the generically described apolipoprotein E truncation mutants used to lower cholesterol, the function of these apolipoprotein E truncation Mutants, and on the effect of these generic truncation mutants on triglyceride levels. Applicants also argue that the Wetterau et al reference fails to provide any basis to conclude that the generic C-terminal apolipoprotein E3 truncation fragment described by McClelland et al is or includes the apolipoprotein E proteolytic fragment consisting of amino acids 1-224, or any of the disclosed fragments of Wetterau et al is biologically active or would retain the biological activity of full length apolipoprotein E3 as required by the methods of McClelland et al., and should be used to treat hypercholesterolemia according to the method of McClelland et al. Neither the Breslow et al reference nor the French et al reference provides remedy for the deficiencies of McClelland et al and/or Wetterau et al. references.

Firstly, McClelland et al disclosed clearly at least a gene therapy method for the treatment of hypercholesterolemia, said method comprises intravenous administering (e.g., portal vein injection or peripheral vein injection) a recombinant replication defective adenoviral vector containing a DNA sequence encoding a human apoliporotein E3 or **a fragment of human apoliporotein E3 that is truncated at the**

C-terminal (page 4, line 5 continues to line 9 of page 6; page 9, third paragraph) in a mammalian host, including a human host (page 8, last paragraph). **The examiner simply relied on the Wetterau et al. reference for what is known in the prior art for the term "the C-terminal of apolipoprotein E3". "The C-terminal" of a human apolipoprotein E3 is made up of amino acid residues 225-299 as evidenced by the teachings of Wetterau et al** (see at least the abstract). **Therefore, the encoded human apolipoprotein E3 fragment that is truncated at the C-terminal taught by McClelland et al is an encoded human apolipoprotein E3 fragment that lacks amino acid residues 225-299**.

Secondly, please note that the Wetterau et al and Breslow et al. references were cited as evidence for the teachings of McClelland et al. The only missing teaching in the McClelland et al reference in the above 103 (a) rejection is administering the vector to an artery at the site of a lesion, and this missing embodiment is supplemented by the teachings of French et al. The above rejection also provides motivations why an ordinary skilled artisan would have combine the teachings McClelland et al and French et al. There is no evidence of record indicating or suggesting why an ordinary skilled artisan would doubt that a fragment of human apoliporotein E3 that is truncated at the C-terminal would not lower cholesterol in a mammal in need thereof as clearly taught by McClelland et al.

2. Applicants further argue that Wetterau et al reference teaches away from the use of ApoE proteins having carboxy-terminal truncations because the reference

states that apolipoprotein E3 fragments that contain the C-terminal end are more likely to be those that bind to lipoprotein complexes involved in the clearing of cholesterol from the plasma on the basis of the highlighted statements such as "**The precise region or regions of apoE that are the most important for its binding to a lipoprotein surface are not known, although the carboxyl-terminal domain may be a good candidate**", "**[A]lthough the amino terminal domain may have lipid-binding capabilities in certain situations, on very low density lipoprotein the carboxyl-terminal domain of apoE may play an important role in lipid interaction**".

Once again, please note that **the examiner simply relied on the Wetterau et al. reference for what is known in the prior art for the term "the C-terminal of apolipoprotein E3". "The C-terminal" of a human apolipoprotein E3 is made up of amino acid residues 225-299 as evidenced by the teachings of Wetterau et al** (see at least the abstract). Furthermore, there is no "teaching-away" whatsoever by the Wetterau et al reference. The entire reference is on the characterization of human apolipoprotein E3 in aqueous solution, which contains two independently folded structural domains of markedly different stabilities: an amino-terminal domain and a carboxyl-terminal domain, separated by residues that may act as a hinge region (see abstract). **There is no factual evidence indicating that a fragment of human apoliporotein E3 that is truncated at the C-terminal is not capable binding to lipids**. Wetterau et al clearly stated that "Both the isolated model amino- and carboxyl-terminal domains of apoE are capable of binding to dimyristoylphosphatidylcholine (15); thus, **both domains have lipid-binding capabilities**. **The precise region or regions**

of apoE that are the most important for its binding to a lipoprotein surface are not known, although the carboxyl-terminal domain **may be a good candidate**" (page 627, col. 1, last paragraph). It is only **a suggestion and not a factual evidence** that the carboxyl-terminal region of apoE **may be a major lipid-binding region**. Even this statement **does not exclude that a fragment of human apolipoprotein E3 that is truncated at the C-terminal is capable of binding to lipids**.

3. Applicants further argue that there is no reasonable expectation of success to use the truncated ApoE of Wetterau et al in the method of McClelland et al as set forth in the above rejection because Wetterau et al directed the skilled artisan away from the use of apolipoprotein E truncation mutants that lack the C-Terminal residues based on the lipid-associating properties of the C-terminal domain of apolipoportein E3.

Please see the Examiner's rebuttals to Applicant's arguments in the preceding paragraphs. McClelland et al disclosed clearly at least a gene therapy method for the treatment of hypercholesterolemia, said method comprises intravenous administering (e.g., portal vein injection or peripheral vein injection) a recombinant replication defective adenoviral vector containing a DNA sequence encoding a human apoliporotein E3 or **a fragment of human apoliporotein E3 that is truncated at the C-terminal** (page 4, line 5 continues to line 9 of page 6; page 9, third paragraph). The results of this application also confirmed the teachings of McClelland et al. Furthermore, **there is no factual evidence indicating that a fragment of human**

apoliporotein E3 that is truncated at the C-terminal is not capable binding to lipids. Therefore, an ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of McClelland et al as evidenced by Wetterau et al, Breslow et al and in view of French et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Amended claims 83-91 and 94-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Strittmatter et al (US 5,811,243) in view of Kahn et al. (US 6,756,523) and Breslow et al (J. Biol. Chem. 257:14639-14641, 1982; Cited previously) for the same reasons already set forth in the Office Action mailed on 5/31/2007 (pages 21-23). ***The same rejection is restated below.***

Strittmatter et al disclosed at least a method comprising intravenous administering to a subject, including a human, combating Alzheimer's disease any suitable viral vector which carries a nucleic acid encoding ApoE (including ApoE1-ApoE4) or ApoE fragments (e.g., ApoE3 fragments 1-191, 1-244, 1-266 and 1-272) (see at least Summary of the Invention; col. 3, lines 52-64; col. 4, lines 33-50; col. 5, lines 30-60; col. 6, lines 49-62). It is noted that lowering cholesterol level is desirable in any mammal, particularly for an adult human, and even more for a human patient at age about 80 years old and combating Alzheimer's disease. Therefore, the treated subject by the method taught by Strittmatter et al would fall within the broad scope of a mammal in need of lowering cholesterol and also at risk for developing atherosclerosis.

Strittmatter et al does not teach specifically the use of a replication-defective adenoviral vector or ApoE3 having SEQ ID NO:2, even though the reference discloses that any suitable viral vector and any ApoE, including ApoE3 and its fragments can be used.

However, at the effective filing date of the present application, Kahn et al already taught the use of a recombinant replication defective adenovirus vector for the expression of selected nucleotides in the cells of the central nervous system (see at least col. 3, lines 1-54).

Additionally, Breslow et al already cloned a human apolipoprotein E3 cDNA having 100% sequence identity to SEQ ID NO:15 (SEQ ID NO:2 plus its signal sequence) of the present invention (see at least Fig. 3 and the attached sequence search).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method of Strittmatter et al by also using a replication defective adenoviral vector containing a DNA sequence encoding ApoE fragments (e.g., ApoE3 fragments 1-191, 1-244, 1-266 and 1-272), including a DNA sequence encoding human ApoE3 fragments obtained from the human cDNA clone taught by Breslow et al. in light of the teachings of Kahn et al. and Breslow et al.

An ordinary skilled artisan would have been motivated to carry out the above modifications because Kahn et al already taught various advantages for using a recombinant replication defective adenovirus such as its great efficacy of infection, long term expression, wide host range and low toxicity (col. 3, lines 1-11). Additionally, the

human ApoE3 cDNA was already available and cloned in the prior art since 1982. The modified method resulting from the combined teachings of Strittmatter et al., Kahn et al. and Breslow et al. is indistinguishable from the methods as broadly claimed because it has the same method steps and starting materials.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Strittmatter et al., Kahn et al. and Breslow et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Amendment

Applicant's arguments related to the above rejections in the Amendment filed on 10/03/07 (pages 21-26) have been fully considered, but they are respectfully not found persuasive for the reasons discussed below.

1. Applicants argue that the Strittmatter et al. reference discloses a method that is not intended to treat high cholesterol levels in the patient, nor is there any mention of this effect, rather the methods of Strittmatter et al are for the sole purpose of "inhibiting the formation of paired helical filaments and/or neurofibrillary tangles". Neither the Kahn et al reference nor the Breslow et al. reference cures the deficiencies of Strittmatter et al reference.

As written, **the claims do not require the mammal to be treated already has a high cholesterol level with respect to a control mammal**. The claims simply require

the treated mammal in need of lowering its endogenous cholesterol level, not necessarily limited to a mammal having a high cholesterol level with respect to a mammal with a normal cholesterol level. As such, the breadth of "a mammal in need of lowering cholesterol" **includes any mammal subjected to the same method steps and starting materials as recited in the method as claimed**. Accordingly, the treated subject by the method taught by Strittmatter et al would fall within the broad scope of a mammal in need of lowering cholesterol of the present invention. Therefore, the modified method resulting from the combined teachings of Strittmatter et al., Kahn et al. and Breslow et al. is indistinguishable from the methods as broadly claimed because it has the same method steps and starting materials. The treated Alzheimer's patients in the modified method would have lowered cholesterol level relative to the cholesterol level before the treatment, in addition to attaining the desired effect of inhibiting the formation of paired helical filamenst and/or neurofibrillary tangles.

2. With respect to the issue of the Office's Official notice of facts not on the record to establish the present obviousness rejection regarding to the limitation "lowering cholesterol level in a mammal in need thereof", Applicants argue the Office without evidence has taken official notice that 1) Alzheimer's disease patients have high cholesterol levels that require lowering and are at risk of developing atherosclerosis, and 2) the skilled artisan's knowledge of this condition in Alzheimer's disease patients, coupled with the disclosures of Strittmatter et al., Kahn et al., and Breslow et al., provides the motivation and reasonable expectation of success to apply the method of

Strittmatter et al to treat high cholesterol in these Alzheimer's disease patient. These factual assertions are not properly official noticed or not properly based upon common knowledge because the factual assertions are made without any evidentiary support.

Please note that the Examiner does not assert that Alzheimer's patients have high or elevated cholesterol levels relative to the normal cholesterol level. The claims simply require the treated mammal in need of lowering its endogenous cholesterol level, not necessarily limited to a mammal having a high cholesterol level with respect to a mammal with a normal cholesterol level. As such, the breadth of "a mammal in need of lowering cholesterol" **includes any mammal subjected to the same method steps and starting materials as recited in the method as claimed**. Accordingly, the treated subject by the method taught by Strittmatter et al would fall within the broad scope of a mammal in need of lowering cholesterol of the present invention. Therefore, the modified method resulting from the combined teachings of Strittmatter et al., Kahn et al. and Breslow et al. is indistinguishable from the methods as broadly claimed because it has the same method steps and starting materials.

Conclusions

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

QUANG NGUYEN, PH.D.
PRIMARY EXAMINER